IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

ESSEX et al.	)	
	)	
v.	)	Interference No. 102,432
	)	
LUCIW et al.	)	Examiner-in-Chief: Caroff
	)	

DECLARATION OF STELLA QUAN, Ph.D.

Box Interference
Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

I, STELLA QUAN, hereby declare that:

1. I am a scientist employed by Chiron Corporation, where I am a Principle Scientist in the Diagnostic Development Division.

2. I hold a Ph.D. in Biochemistry from Massachusetts Institute of Technology, and have over 14 years experience in directing and conducting research in the field of medical diagnostics utilized for the detection of infectious diseases. I have authored or co-authored over 10 scientific publications. Attached hereto is my Curriculum Vitae, which lists these publications. I have over 9 years of experience in the immunology of infectious diseases, including the development of immunodiagnostics, and am familiar with the state of the art as of October 1984.

3. It is my expert opinion that the state of the art in October 1984 was at best speculative with respect to the general usefulness of recombinant antigens in immunoassays. For a particular virus, there may be factors that prevent development of an effective immunoassay using a recombinant antigen. These factors can be genuine stumbling blocks which cannot be predicted with any degree of certainty. A case which exemplifies that producing a successful recombinant immunoassay is not merely a hypothetical problem is illustrated by the work at Chiron with the Hepatitis A Virus (hereinafter "HAV").

4. Prior to my involvement, I am informed and believe that Chiron's work on a recombinant HAV antigen began in mid 1985 when the first effort to construct a full length HAV clone was attempted. By 1987, Chiron had extended the research effort to include four Ph.D. scientists and several laboratory assisting personnel. Experiments showed that purified HAV protein produced by recombinant DNA techniques, while antigenic in animals, failed to elicit neutralizing antibodies or protective immunity in experimental animals. These proteins expressed in a variety of systems (e.g; bacteria and yeast) did not have neutralizing epitopes.

5. HAV is a non-enveloped, icosahedral virus carrying a single-stranded RNA genome of approximately 7,500 bases in length. The RNA is translated as a single polyprotein of about 250,000 daltons that is subsequently cleaved to generate the viral capsid and non-capsid proteins. The capsid protein was a logical target of our recombinant work because it is functionally equivalent to the envelope protein of other viruses in that it is the outermost protein of the virion; i.e. the first protein that is presented to or recognized by the immune system.

6. In May 1987, I began work on fulfilling a Chiron company goal of developing a diagnostic assay for HAV. Initial

attempts included using existing recombinant material prepared by the HAV research group and native protein. As additional recombinant material was made available to me, I continued to work towards developing a recombinantly based HAV immunoassay. In working with recombinant HAV capsid protein, however, it was discovered that the polypeptides that had been recombinantly expressed did not exhibit epitopes that were required to develop a successful recombinantly based HAV immunoassay. Over a period of several years, I received a variety of recombinant antigens from collaborating groups at Chiron and continued my attempts to develop a workable immunoassay implementing a variety of conditions. I tried every available alternative which was obvious to me. The immunoassay I was attempting to develop would detect antibodies to HAV in human serum. I hoped that a recombinant HAV antigen, bound to a solid support, would function in a competitive or sandwich ELISA format. These efforts to produce recombinant HAV useful in an immunoassay were unsuccessful. Virtually no antibodies in human serum bound the recombinant capsid antigen, even though it was antigenic in animals; i.e., it elicited antibodies upon injection. I have since abandoned research in development of an immunoassay based on the recombinant HAV capsid antigen. For whatever reason, recombinant antigen-based HAV immunoassays did not work. My involvement in the project to develop a recombinant antigen based immunoassay for HAV ultimately ended in early 1990.

7. Based upon the above experience, it is my expert opinion that the functionality of a recombinant protein antigen in an immunoassay is not generally predictable. Certainly it must be concluded that the ability of a recombinant antigen to bind diagnostically useful antibodies is not predictable. With respect to a newly discovered virus, there would be very little basis to predict whether recombinant antigens could be successfully employed in an immunoassay. If quantifiable, the level of predictability would be significantly less that 50%.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

March 8, 1991
Date

Stella Quan
Stella Quan, Ph.D.

ATTACHMENT
TO THE DECLARATION OF
STELLA QUAN, Ph.D.

STELLA QUAN
93 Sullivan Drive
Moraga, CA 94556
(415)376-3801

EDUCATION

1974 Ph.D. Biochemistry, Massachusetts Institute of Technology
1969 B.S. Chemistry, University of California

PROFESSIONAL EXPERIENCE

1987-Present Principal Scientist III, Chiron Corporation, Emeryville, CA

- Responsible for successful completion of immunoassays for detection of infectious diseases based on recombinant antigens or virus
- Coordinated activities for clinical trials and PMA submission
- Planned production facility for manufacture of 40 million tests per year
- Developed unique procedure for increasing viral immunoreactivity and contributed to significant cost reduction for the product

1986-1987 Project Manager, 3M Diagnostic Systems, Mountain View, CA

- Directed research and development of immunodiagnostic kits for allergy test and obtained 510K approval to market the assays
- Directed the Manufacturing Department for six months and resolved manufacturing problems related to microtiter well coating and stability

1985-1986 Senior Scientist II, 3M Diagnostic Systems

- Developed novel immunoassays for allergy testing
- Developed multiple controls for allergen specific IgE and IgGa's

1982-1985 Project Manager, SmithKline Instruments, Sunnyvale, CA

- Directed nine research scientists in the development of unique immunoassays for doctor's office

1980-1982 Senior Research Associate, SmithKline Instruments

- Responsible for the development of coagulation and liquid chemistry reagents

STELLA QUAN

1977-1980 Research Scientist, SmithKline Instruments

- Responsible for the development of chemistry reagents for acid phosphatase, kinetic and end-point triglyceride, cholesterol, uric acid, creatine kinase, ALT, AST and iron/iron binding capacity

1976-1977 Research Associate, Massachusetts Institute of Technology

- Carried out research on isolation of amino acid auxotrophs with genetically altered aminoacyl tRNA synthetase
- Purified and characterized a new protein that binds to tyrosine tRNA and has a unique regulation role in the metabolism of tyrosine

1974-1976 Postdoctoral Fellow, University of California, San Francisco

- Research on mechanism of interaction of FdUMP and folate with thymidylate synthetase
- Research on new chemical synthesis for altering the oxygen affinity of hemoglobin to find a cure for sickle cell anemia

PUBLICATIONS

1) "Equilibrium Measurements of Cognate and Noncognate Interactions Between Aminoacyl Transfer RNA Synthetase and Transfer RNA". Biochem. (1975) 14, 2775.

2) "Two Photo-Crosslinked Complexes of Isoleucine Specific Transfer RNA with Aminoacyl Transfer RNA Synthetases". J. Biol. Chem. (1975) 280, 4433.

3) "In Vitro Studies of Photochemically Crosslinked Protein-Nucleic Acid Complexes. Determination of Crosslinked Regions and Structural Relationships in Specific Complexes". Aging, Carcinogenesis, and Radiation Biology (1976) 123.

4) "Thymidylate Synthetase: Fluorine-19 NMR Characterization of the Active Site Peptide Covalently Bound to 5-Fluoro-2'-Deoxyuridylate and 5, 10-methylene-tetrahydrofolate". Biochem. Biophys. Res. Comm. (1976) 72, 404.

5) "Thymidylate Synthetase: Interaction with 5-Fluro and 5-Trifluromethyl-2'-Deoxyuridylic Acid". ACS Symposium Series (1976) 23, 57.

6) "An improved Reagent for Kinetic/Endpoint Determination of Triglyceride with an Enzymatic Procedure Adapted for both Manual and Automated Applications". Clin. Chem (1981) 27, 1040.

7) "Prostatic Acid Phosphatase by Colorimetric Kinetic Assay with Improved Sensitivity". Clin. Chem (1981) 27, 1062.

8) "Double Antibody Kinetic Immunoassay for Prostatic Acid Phosphatase Measurement". Clin. Chem. (1982) 28, 1558.

9) "HCV Additional Testing". Proceedings of First International Symposium Hepatitis C Virus (1990), 25.

10) "HCV Testing in Low-risk Population". Lancet (1990) 336, 695.

11) "Confirmation of Hepatitis C Virus Infection by New Four-antigen Recombinant Immunoblot Assay". Lancet (1991) 337, 317.